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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SUSANNE MATHEUS and HANNS-CHRISTIAN MAHLER

Appeal 2010-012173
Application 10/588,458
Technology Center 1600

Before TONI R. SCHEINER, ERIC GRIMES, and MELANIE L. McCOLLUM, *Administrative Patent Judges.*

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 4, 8, 11, 16, 17, and 21-24, directed to a process for preparing a highly concentrated, liquid formulation of a monoclonal antibody. The claims have been rejected on the grounds of obviousness and indefiniteness. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Claims 1, 4, 8, 11, 16, 17, and 21-24 are on appeal. Claims 18-20 have been withdrawn from consideration, and claims 2, 3, 5-7, 9, 10, and 12-15 have been canceled. Appellants have not presented separate arguments for the claims, therefore, we select claim 1 as representative of the claimed subject matter. 37 C.F.R § 41.37(c)(1)(vii). Claim 1 is as follows:

> 1. A process for the preparation of a highly concentrated, liquid formulation comprising monoclonal antibody c225 (Mab c225) or monoclonal antibody h425 (Mab h425), comprising ultrafiltering a preparation comprising said Mab c225 or Mab h425, wherein the concentration of said antibody in said highly concentrated, liquid formulation thus prepared is 50 mg/ml to 180 mg/ml.

The Examiner relies on the following evidence:

Arvinte et al. WO 02/096457 A2 Dec. 5, 2002

Srikala S. Sridhar et al., *Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer,* 4 THE LANCET ONCOL. 397-406 (2003).

DANIEL P. STITES ET AL., BASIC & CLINICAL IMMUNOLOGY 317 (8th ed. 1994).

In addition, Appellants rely on the following evidence:

Lam et al. US 6,171,586 B1 Jan. 9, 2001

The Examiner rejected claims 1, 4, 8, 11, 17, and 22-24 under 35 U.S.C. § 103(a) as unpatentable over Sridhar and Arvinte.

In addition, the Examiner maintained the rejection of claims 16 and 21 under 35 U.S.C. § 112, second paragraph, as indefinite.

Finally, the Examiner's provisional rejection of claims 1, 3, 5-10, and 12-17 on the ground of non-statutory obviousness-type double patenting

over claims 1-13, 15-24, 26, and 27 of Application No. 10/996,597 is moot, as the application has been abandoned.

OBVIOUSNESS

Issue

The Examiner finds that Sridhar discloses a clinical trial of cetuximab (IMC-C225), a human-murine chimeric monoclonal antibody that targets EGFR, but the reference doesn't disclose the required "antibody formula concentration or the means of concentrating an antibody formulation" (Ans. 6). However, the Examiner finds that Arvinte discloses highly concentrated formulations of antibodies "of at least 50 mg/ml up to 250 mg/ml and methods of making them by ultrafiltration" (*id.*). In addition, the Examiner finds that Arvinte teaches that the "antibodies may be monoclonal, including chimeric antibodies which are humanized, antibody fragments and [PEGylated] antibody derivatives" (*id.* at 7).

The Examiner concludes that it would have been obvious for one of ordinary skill in the art to prepare a highly concentrated formulation of cetuximab by ultrafiltration (*id.*), because Arvinte teaches that there is a demand in the market for highly concentrated, liquid antibody formulations suitable for the small volumes required by pre-filled delivery devices (*id.* at 6), and because Arvinte teaches that ultrafiltration is "part of a general method for preparation of high[ly] concentrated liquid formulations" (*id.* at 7).

Appellants contend that "highly concentrated, liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large proteins with specific properties, such as, monoclonal antibodies that are usable in the

clinical setting" (App. Br. 5). Appellants also contend that "nothing [in the references] motivates a skilled worker to choose precisely Mab c225 . . . and combine it with precisely a generic process of concentrating proteins" (*id.*).

The issue raised by this appeal is whether the Examiner has established that it would have been obvious for a person of ordinary skill in the art to prepare a highly concentrated formulation of Mab c225 by ultrafiltration, given the teachings of Sridhar and Arvinte.

Fact Findings

Appellants do not dispute the Examiner's fact findings as set forth on pages 6 and 7 of the Answer, and we adopt them as our own.

Principles of Law

[The obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." (*Id.* at 418-19. To paraphrase *KSR*, if a technique has been used to improve one process or product, and a person of ordinary skill in the art would recognize that it would improve similar processes or products in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Id.* at 417.

Discussion

We will affirm this rejection as we agree with the Examiner that it would have been obvious for a person of ordinary skill in the art to prepare a highly concentrated formulation of Mab c225 by ultrafiltration, given the teachings of Sridhar and Arvinte, for the reasons explained in the Answer. We are not persuaded otherwise by Appellants' arguments.

Appellants contend that "the present invention is directed to the preparation of highly concentrated, liquid formulations of Mab c225 [or] Mab h425 as stable, ready-to-use solutions having low viscosity, low application volumes (for use as pharmaceutical preparations) . . . that are applicable for subcutaneous administration" (App. Br. 5). Appellants contend that "highly concentrated, liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large proteins with specific properties" (*id.*). Appellants cite the background portion of Lam as evidence that it was generally "recognized that monoclonal antibodies pose[ ] a difficult problem with respect to high concentrations, especially if pharmaceutically critical stabilizers should be omitted" (*id.*, emphasis omitted), and further contend that "a specific method has to be developed to arrive at a preparation of highly concentrated formulations" (*id.*). Appellants argue that "proceeding contrary to the accepted wisdom in the art is evidence of non-obviousness" (*id.*).

These arguments are not persuasive. As noted by the Examiner, the claims are not limited to a formulation with any particular viscosity other than "liquid," the claims don't preclude the presence of stabilizers in the formulation, and the only step required by the claims is "ultrafiltering" (Ans.

7). Moreover, while it may be generally true that concentrating some large proteins poses untoward technical problems, and that "proceeding contrary to accepted wisdom" can be evidence of non-obviousness, we agree with the Examiner that Appellants have not established that there were any particular problems in developing a method of preparing a formulation of Mab c225 with the requisite concentration, or that they were required to "proceed[ ] contrary to the accepted wisdom of the prior art" in order to do so (*id.* at 8). As the Examiner puts it, this "is a case in which the artisan of ordinary skill would have recognized the substitution of one known antibody for another yielding predictable results" (*id.*).

Appellants also contend that Arvinte's monoclonal anti-IgE antibody "bind[s] *to a very broad target*" and therefore, "is not equivalent to c225 or h425 monoclonal antibodies . . . which are characterized by specific epitope-binding capability" (App. Br. 6).

This argument is not persuasive. We agree with the Examiner that Appellants have not established that the particular specificity of the antibody has a bearing on its concentration by ultrafiltration (Ans. 8).

Finally, Appellants contend that nothing in the prior art would have motivated one of skill in the art to "to choose precisely Mab c225 or h425 and combine it with precisely a generic process of concentrating proteins" (App. Br. 5).

Nevertheless, we are in complete agreement with the Examiner that the fact that Mab c225 was "in clinical trials for cancer treatment" (Ans. 9) "would have made it an obvious choice for concentrating for injectable liquid formulation" (*id.* at 10).

INDEFINITENESS

Appellants have not responded to the Examiner's rejection of claims 16 and 21 as indefinite under 35 U.S.C. § 112, second paragraph.

The rejection is summarily affirmed.

SUMMARY

The rejection of claims 1, 4, 8, 11, 17, and 22-24 as unpatentable over Sridhar and Arvinte is affirmed.

In addition, the rejection of claims 16 and 21 as indefinite is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc